In the Specification:

Please replace the paragraphs indicated below with the following paragraph:

[0018] One method of identifying inhibitors of the p53/HDM2 protein complex is to determine the amino acid specificities of HDM2 binding pockets by crystallography in order to establish a model for the interaction. Using this method, Kussie et al. identified p53 based peptide antagonists (Kussie, P.H. et al., Science 274:948-953 (1996)). Kussie et al. disclosed the crystal structure of the 109-amino-acid NH2-terminal domain of MDM2, which contains the p53 binding activity, bound to a peptide from the transactivation domain of p53. In particular, Kussie et al. disclosed:

> Crystals of the human MDM2 (residues 17 to 125)-p53 (residues 15 to 29) complex grew as tightly clustered thin plates, and successive rounds of macroseeding were required to obtain single crystals suitable for diffraction. To circumvent this problem, crystals of Xenopus laevis MDM2 [residues 13 to 118; 71 percent identity to human MDM2 (28)] bound to human p53 (residues 13 to 29), which grew readily, were used for the structure determination by the multiple isomorphous replacement (MIR) method (Fig. 1 and Table 1) (29). The structure of the human MDM2-p53 complex was then determined by molecular replacement using the 2.3 Å structure of the X. laevis complex (R factor of 18.8 percent) as a model, and it was refined at 2.6 Å resolution to an R factor of 20.0 percent (Table 1) (29).

~~A crystal structure of a truncated form of HDM2 (residues 17-125) and a 15'mer peptide derived from the N-terminal transactivation domain of p53 was published by Kussie et al. (Kussie et al., (1996)). Kussie et al. also published a crystal structure of MDM2 (Kussie et al., (1996)) derived from Xenopus laevis (residues 13 to 118), having a 71% sequence identity towards HDM2.~~ Based on molecular modeling, Garcìa-Echeverrìa et al. published a model of an 8'mer peptidomimetic, derived from the 15'mer wild-type p53 peptide, bound to the N-terminal domain of hdm2 (Garcìa-Echeverrìa, C. et al., J. Med. Chem. 43:3205-3208 (2000)). No crystal structure of HDM2 with inhibitory compounds, such as small molecule inhibitors, for example, or other peptides is believed to have been disclosed.

[0033] FIG. 1 Ribbon representation of HDM2 (SEQ ID NO:2) bound to compound 338437.

[0034] FIG. 2 Fit of compound 338437 into the active site of HDM2 (SEQ ID NO:2) represented as a molecular surface.

[0035] FIG. 3 Ribbon representation of a superposition between hdm2 (SEQ ID NO:2) in the trigonal crystal form and in the tetragonal form. The RMS deviation between C-alpha atom positions is 0.25 Angstroms.

[0200] cDNA encoding residues 17-125 of HDM2 (amino acids 17-125 of SEQ ID NO:1) were cloned and expressed as follows: PCR was performed using ATCC item number 384988 containing partial human MDM2 sequence as template and the following primers:

Forward: 5'-CTCTCTCGGATCCCAGATTCCAGCTTCGGAACAAGAG (SEQ ID NO:5)

Reverse: 5'-TATATATCTCGAGTCAGTTCTCACTCACAGATGTACCTGAG (SEQ ID NO:6).

[0202] For HDM2 23-114 (SEQ ID NO:3), the primers used were as follows:

5'-CGACGATTGGATCCGAACAAAGACCCTG (SEQ ID NO:7)

3'-GGCTACTACTCCGAGTCATTCCTGCTGATTGACTAC (SEQ ID NO:8)

[0203] For HDM2 17-111 (SEQ ID NO:2), the primers used were

5'-CTCTCTCGGATCCCAGATTCAGCTTCCGGAACAAGAG (SEQ ID NO:9)

3'-TTCAGCAGCTCGAGTCAATTGACTACTACCAAGTTC (SEQ ID NO:10)

[0208] HDM2 17-111 (SEQ ID NO:2) was complexed with the compound of interest by dialysis at a concentration of 0.7 mg/ml, the buffer brought to 20 mM HEPES pH. 7.4, 100 mM NaCl, 5 mM DTT, filtered through a 0.02 .mu.m filter, and concentrated to 10 mg/ml.

[0212] The inhibition of MDM2 binding to p53 was measured using a p53 peptide analog binding to MDM2 residues 17-125 of SEQ ID NO:1. The published crystal structure of this complex (Kussie, P. H., et al., Science 274:948-953 (1996)) validates this fragment as containing the p53 binding site, and we have solved the X-ray structure of the p53 peptide analog MPRFMDYWEGLN (SEQ ID NO:11), described to be a peptide inhibitor of the MDM2 p53 interaction (Bottger, A., et al., J Mol Biol 269:744-756 (1997)). The assay uses N terminal fluorescein RFMDYWEGL (SEQ ID NO:12) peptide (F1 9 mer). Compound was incubated for 15 minutes with 30 nM fluorescein peptide F1 9 mer and 120 nM HDM2 17-

125 of SEQ ID NO:1 in 50 mM HEPES pH. 7.5, 150 mM NaCl, 3 mM octyl glucoside. The polarization of the fluorescein label was measured by excitation at 485 nm and emission at 530 nm. Polarization was expressed as a percent of a no compound control, using no MDM2 with Fl 9 mer as background.

[0213] HDM2 (SEQ ID NO:2) Atomic Coordinates: Table 1 (Compound 1)

[0215] HDM2 (SEQ ID NO:2) Atomic Coordinates: Table 2 (Compound 2)

[0217] HDM2 (SEQ ID NO:2) Atomic Coordinates: Table 3

[0219] The pdb-format is described on various sites on the web. Depending on the program crystallographic application minor modifications to this format may be found. A good primer is provided by this link at CCP4 ~~"www.ccp4.ac.uk/html/pdbformat.html"~~. A more extended description can be found at the RCSB home page.